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ORIGINAL REPORT

Randomized Trial of Two Intravenous Schedules of the Topoisomerase I Inhibitor Liposomal Lurtotecan in Women With Relapsed Epithelial Ovarian Cancer: A Trial of the National Cancer Institute of Canada Clinical Trials Group

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ABSTRACT

Purpose

Liposomal lurtotecan (OSI-211) is a liposomal formulation of the water-soluble topoisomerase I inhibitor lurtotecan (GI147211), which demonstrated superior levels of activity compared with topotecan in preclinical models. We studied two schedules of OSI-211 in a randomized design in relapsed ovarian cancer to identify the more promising of the two schedules for further study.

Patients and Methods

Eligible patients had measurable epithelial ovarian, fallopian, or primary peritoneal cancer that was recurrent after one or two prior regimens of chemotherapy. Patients were randomly assigned to receive either arm A (OSI-211 1.8 mg/m^2/d administered by 30-minute intravenous infusion on days 1, 2, and 3 every 3 weeks) or arm B (OSI-211 2.4 mg/m^2/d administered by 30-minute intravenous infusion on days 1 and 8 every 3 weeks). The primary outcome measure was objective response, which was confirmed by independent radiologic review, and a pick the winner statistical design was used to identify the schedule most likely to be superior.

Results

Eighty-one patients were randomized between October 2000 and September 2001. The hematologic toxic effects were greater on arm A than on arm B (grade 4 neutropenia, 51% *v* 22%, respectively), as was febrile neutropenia (26% *v* 2.4%, respectively). Of the 80 eligible patients, eight patients (10%) had objective responses; six responders (15.4%; 95% CI, 6% to 30%) were in arm A and two responders (4.9%; 95% CI, 1% to 17%) were in arm B.

Conclusion

The OSI-211 daily for 3 days intravenous schedule met the statistical criteria to be declared the winner in terms of objective response. This schedule was also associated with more myelosuppression than the schedule of OSI-211 administered in arm B.

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INTRODUCTION

Ovarian cancer is the fifth most common cause of cancer-related deaths in Canada and the United Kingdom, and it has the highest mortality rate of all the gynecologic malignancies. Disease that recurs after first-line treatment is incurable, and although most ovarian tumors initially respond to chemotherapy, eventually the disease becomes resistant to treatment. The main factor that influences the choice of treatment is

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the time from previous chemotherapy. The treatment-free interval has consistently been the most important factor in predicting future response.[1-4] Patients with disease that recurs within 6 months of first-line therapy have a low response rate when re-treated with the same chemotherapy and are considered relatively resistant to the original drugs. Recurrences 6 or more months after completion of front-line therapy are associated with higher rates of response to platinum compounds or other active agents, with response rates approaching 60% when the interval is at least 24 months.[5]

The topoisomerase I inhibitor topotecan has become established as an active drug in recurrent ovarian cancer. In a large, multicenter, phase II study, topotecan demonstrated response rates of 5.9% in patients with recurrent disease within 6 months of previous treatment and 17.8% in patients whose progression-free interval was greater than 6 months.[6] A phase III randomized trial comparing topotecan with paclitaxel showed that the response rate was similar for both drugs in patients who had received prior platinum therapy (response rate, 20.5% for topotecan and 13.2% for paclitaxel). Median survival time was 61 weeks for topotecan and 43 weeks for paclitaxel ($P = .515$).[7] The cross-over response rate was 13.1% for topotecan and 10.2% for paclitaxel, indicating a degree of non–cross-resistance between these two drugs.[8] The activity of topotecan in ovarian cancer is schedule-dependent. Using a "pick the winner design,"[9] a randomized phase II trial of a 24-hour weekly infusion of topotecan versus five daily bolus injections showed responses rates of 3.1% and 22.6%, respectively, demonstrating that the 5-day schedule is the preferred option.[10]

Clearly, a formulation that delivers a prolonged exposure to a topoisomerase I inhibitor without necessitating five daily intravenous injections could present an advantage should it retain or surpass these levels of activity. Liposomal lurtotecan (OSI-211) is a liposomal formulation of the water-soluble topoisomerase I inhibitor lurtotecan (GI147211). Lurtotecan has demonstrated similar levels of activity to topotecan in preclinical models[11,12] and has shown activity similar to topotecan in a daily for 5 days schedule in relapsed ovarian cancer.[13] In preclinical models, OSI-211 was compared with unencapsulated lurtotecan and produced a 1,000-fold greater area under the curve (AUC) of total lurtotecan derived from OSI-211 and a half-life of five-fold longer.[14] Furthermore, the therapeutic index of single-dose OSI-211 in preclinical models was three- to 14-fold greater than that of lurtotecan or topotecan. Therefore, OSI-211 was of interest to investigate in the clinic.

Phase I trials of OSI-211 have evaluated several schedules of administration and have recommended phase II regimens of 2.4 mg/m^2/d on days 1 and 8 and 1.8 mg/m^2/d for 3 days.[15] Data from pharmacokinetic studies using prolonged exposure to low levels of lurtotecan indicate a relationship between the amount of lurtotecan excreted renally and hematologic toxicity, suggesting that prolonged exposure may be achieved.[16] These pharmacokinetic results differ markedly from the results observed when nonliposomal lurtotecan is administered.[17] Ideally, this could translate into efficacy that could be detected on an infrequent (eg, days 1 and 8) schedule of administration, obviating the need for repeated daily dosing. But before abandoning repeated daily dosing with this formulation of a topoisomerase I inhibitor, clinical evidence confirming that this was appropriate seemed important to obtain. Because both the days 1 and 8 schedule and the daily for 3 days schedule produced similar dose-limiting hematologic effects and, importantly, both showed evidence of antitumor effects in ovarian cancer, we undertook a randomized trial of both schedules in relapsed ovarian cancer to assess their toxicity and antitumor efficacy. A pick the winner design was used to maximize the probability of selecting the better of the two schedules for further evaluation in ovarian and other cancers.[9]

PATIENTS AND METHODS

Eligibility

Eligible patients were to have histologically documented epithelial ovarian, primary fallopian, or peritoneal cancer for which they had received one or two prior regimens of chemotherapy (at least one platinum-containing regimen). Patients were required to have unidimensionally measurable disease, an Eastern Cooperative Oncology Group performance status of 0 to 2, age older than 18 years, life expectancy more than 12 weeks, neutrophils more than 1.5×10^9/L, platelet count more than 100×10^9/L, serum creatinine less than 1.5× the upper normal limit (UNL), bilirubin less than UNL, and AST and/or ALT less than 2.5× the UNL. Patients must have been at least 4 weeks from their last chemotherapy treatment to be eligible. Patients were excluded from the study if they had received prior treatment with topotecan or other topoisomerase I inhibitor, had a prior malignancy other than ovarian cancer, or had any severe uncontrolled comorbidity. Signed informed consent was obtained from all patients before randomization, and the study protocol received ethical approval from the research ethics board of each participating hospital before trial activation.

Investigations and Treatment

Baseline investigations included medical history, physical examination, CBC, biochemistry, creatinine and liver function tests, CA-125, ECG, chest x-ray, and computed tomography imaging of the abdomen and pelvis. Patients were stratified by time from last treatment (< 6 v > 6 months) and number of prior regimens (one v two regimens) and then randomized centrally by the Clinical Trials Group of the National Cancer Institute of Canada. The two treatment schedules were as follows: arm A, OSI-211 1.8 mg/m^2/d administered by 30-minute intravenous infusion on days 1, 2, and 3 every 3 weeks; and arm B, OSI-211 2.4 mg/m^2/d administered by 30-minute intravenous infusion on days 1 and 8 every 3 weeks. OSI-211 (supplied initially as NX211 by Gilead Sciences, Foster City, CA) is a sterile liposomal dispersion of lurtotecan in a buffer

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composed of 10 mmol/L ammonium chloride and 9% sucrose in vials containing 5 mg/10 mL. The calculated dose was added to 5% dextrose for injection in a total volume of approximately 25 mL. The diluted drug was then infused intravenously over 30 minutes using a controlled rate pump.

Treatment was to be continued for two cycles after documented confirmation of complete response or four cycles after documented partial response (or until disease progression at the investigators discretion). For patients with stable disease, a maximum of six cycles was administered. At cycle 2, patients who did not experience significant toxicity during cycle 1 were to be dose escalated (Table 1). The escalated dose was to be maintained for all subsequent cycles, provided that the patient did not meet the criteria for dose reduction. To be eligible for dose escalation, patients required nadir neutrophils $\geq 1.0 \times 10^9$/L, nadir platelets $\geq 75 \times 10^9$/L, no major organ toxicity more than grade 1, and no other symptomatic toxicity more than grade 2.

Dose adjustments were made according to the nadir blood counts and worst toxicity of the previous cycle. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria (version 2.0), and patients who had dose reductions because of toxicity did not have the dose re-escalated. Treatment continued on time, provided that the neutrophil count was $\geq 1.5 \times 10^9$/L and platelet count was $\geq 100 \times 10^9$/L; otherwise, treatment was delayed by 1-week intervals until count recovery. If there was no recovery after a 2-week delay, the patient was taken off the study. The dose levels and adjustments are listed in Table 1. Patients who experienced grade 3 or 4 major organ toxicity would have their dose reduced by one dose level. Patients who had a nadir neutrophil count less than 0.5×10^9/L for 7 or more days or an episode of febrile neutropenia and/or a platelet count less than 25×10^9/L or thrombocytopenia bleeding would have their dose reduced by one level. The treatment on day 8 (arm B only) was omitted if the neutrophil count was $\leq 1.0 \times 10^9$/L or the platelet count was less than 75×10^9/L. Treatment was discontinued if there was unacceptable toxicity or demonstration of disease progression or new disease. CA-125 increase alone was not considered disease progression. Hematopoietic growth factor support was not used prophylactically or as a substitute for dose reduction, but usage was at the investigators' discretion.

Before each cycle, patients had a physical examination, CBC, biochemistry, creatinine and liver function tests, and CA-125, and then after each two cycles (or more often if clinically indicated), patients had a chest x-ray and computed tomography imaging of the abdomen and pelvis to observe sites of disease documented at baseline. After completion of protocol treatment, patients were observed for late toxicities at 4 weeks and then every 3 months. Once patients had progressed, continued follow-up was not required except to document late toxicities and death.

Table 1. Dose Levels of OSI-211 for Drug Administration

Treatment Arm	Starting Dose (mg/m^2/d)	Dose Escalation, Level +1 (mg/m^2/d)	Dose Reduction, Level −1 (mg/m^2/d)	Dose Reduction, Level −2 (mg/m^2/d)
Arm A	1.8	2.1	1.5	1.2
Arm B	2.4	2.8	2.0	1.6

Abbreviation: OSI-211, liposomal lurtotecan.

Study End Points

The primary end point of the study was objective tumor response as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.[18] Patients were considered assessable for response provided they had at least one follow-up assessment of disease after start of therapy. After completion of patient accrual, a radiologic review was performed by two independent radiologists on patients with investigator-claimed confirmed or unconfirmed responses as well as other selected nonresponding patients (eg, CA-125 responders and random patients with both stable disease and disease progression). The opinion of the radiology review was considered final in terms of assigning patient response. Responses rates were calculated for the eligible population as well as the assessable population.

Secondary end points included CA-125 response (Gynecologic Cancer Intergroup–modified Rustin definition[19]) and toxic effects assessed using National Cancer Institute Common Toxicity Criteria (version 2.0). All patients were considered assessable for toxicity from the time of their first treatment with OSI-211.

Pharmacokinetic Evaluation

Pharmacokinetic studies were performed during cycle 1 in a subset of separately consenting patients. On the basis of data from phase I trials,[20] a limited sampling approach was used (see Pharmacokinetic Methods). Assays measured total lurtotecan, rather than total free drug, because it was not possible to develop a reliable method of assaying free drug without disrupting the liposome. Furthermore, the fact that nonliposomal lurtotecan is highly protein bound provided additional challenges in assessment. For these reasons, accurate determinations could be made only for total lurtotecan in plasma.

Pharmacokinetic Methods

Samples were taken on day 1 before and at the completion of the OSI-211 infusion and 4 hours after the start of the infusion and on day 2 at 24 hours after the start of the infusion. Four-milliliter blood samples were centrifuged under refrigeration within 30 minutes of collection for 10 minutes to separate plasma. Plasma was dispensed into labeled cryovials and stored at −20°C until shipping to a central laboratory (Analytic Solutions Inc, Sunnyvale, CA) for analysis.

A validated analytic method consisting of high performance liquid chromatography and fluorescence detection was used to determine concentrations of total lurtotecan in plasma samples.[21] In this procedure, the liposomes were disrupted to release all lurtotecan, and any of the carboxylate form was converted to the lactone form of lurtotecan. The internal standard (IS) used was 6,7-dimethoxy-4-methyl-coumarin. Samples were protected from light at all times. Plasma samples were precipitated by the addition of a solution of IS in acetonitrile containing 11.9% glacial acetic acid and were vortexed for 1 minute. The acid assures complete conversion of lurtotecan to its lactone form. The samples were then covered to protect from light and left to stand at room temperature for approximately 2 hours, followed by centrifugation at 13,000 rpm for 10 minutes. The resulting supernatant (20 μL) was injected onto the liquid chromatography system. The chromatographic conditions consisted of an Inertsil ODS-2 (GL Sciences Inc, Tokyo, Japan), 15.0 cm × 46 mm, 5-μm analytic column maintained at 35°C, a mobile phase of 74:26 (volume-to-volume ratio), 50 mmol/L ammonium acetate, acetonitrile (pH 5.5), and a flow of 1 mL/min. Lurtotecan

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and the IS were detected using fluorescence excitation at emission wavelengths of 378 and 420 nm, respectively.

Calibration curves were prepared using lurtotecan at concentrations that ranged from 1 to 500 ng/mL. Samples with concentrations greater than the highest calibrator were diluted in prescreened free-of-interference human plasma. For quality-control samples of OSI-211 in plasma prepared at low, medium, and high and at the assay limit of quantitation, the intra-assay precision (coefficient of variation) and accuracy (bias as percentage of nominal) were less than 5.0% and 93.3% to 107.5%, respectively. The limit of quantitation of the assay was 1 ng/mL. Plasma maximum concentration (C_{max}) was assigned as the concentration observed at the end of infusion, and AUC from time zero to infinity was estimated based on the 4-hour plasma concentration using the limited-sampling model.[20]

Statistical Methods

The primary end point of this study was efficacy as measured by objective response. Instead of the usual randomized study design using a large number of patients to assure the power to detect small differences in outcomes, this study used a pick the winner format based on the approach proposed by Simon et al.[9] As designed, this gave a 90% chance of selecting the better treatment if the difference in response rates was at least 10% and the smaller response rate was assumed to be only 5%. Because a response rate of less than 5% was regarded to be unimportant clinically, a two-stage design was used to allow early termination of ineffective arm(s) early in the study. In the first stage, 20 response-assessable patients were entered onto each arm. If one of the two arms had no responses, accrual to that arm would be terminated, and it would be concluded that that schedule was not interesting. If at least one response was seen in each arm, the trial would continue to the second stage with the accrual of an additional 17 response-assessable patients in both arms (total, 37 patients per arm). If five or more responses were seen in one arm and fewer than five responses were seen in the other arm at the end of the second stage, then the arm with the greatest number of responses would be declared the winner. If neither arm had five responses, both schedules would be considered uninteresting for further evaluation. If both arms had five or more responses, then other factors, such as toxic effects, feasibility, and so on, would contribute to selecting a preferred schedule for further evaluation. No formal statistical comparison between the two arms was planned. The null hypothesis for the response rate was 5% versus an alternative hypothesis of a response rate of 20%. The type I error for each of the arms with this two-stage design was 4%, and the power was 89%. Time to progression and survival were estimated by the product-limit method of Kaplan-Meier.[22]

All eligible patients are included in the description of study results and toxic effects. Objective response rates are presented for both the eligible and the assessable patient populations.

RESULTS

Patient Characteristics

Between October 2000 and September 2001, 81 patients were randomized from 11 participating centers (five in Canada and six in the United Kingdom). After documentation of a partial response in at least one patient in each arm in the first stage of accrual, the trial went to the second stage in both arms. Forty patients were randomly assigned to arm A, and 41 patients were assigned to arm B. One arm A patient was ineligible (no measurable disease at study entry on radiology review), leaving 39 eligible patients in arm A and 41 in arm B. The baseline characteristics are listed in Table 2. In general, the characteristics were well balanced between the two arms. The predominant histology was serous, most patients had a performance status

Table 2. Patient Characteristics

Characteristic	No. of Patients		
	Arm A*	Arm B†	Total
Eligible patients	39	41	80
Age, years			
Median	61	54	58
Range	36-79	31-79	31-79
ECOG performance status			
0	7	12	19
1	28	25	53
2	4	4	8
Malignancy type			
Ovary	34	38	72
Peritoneum	5	3	8
Prior chemotherapy regimens			
1	15	17	32
2	24	23	47
3	0	1	1
Sites of disease			
Abdomen	10	11	21
Ascites	14	13	27
Liver	5	15	20
Lung	2	4	6
Nodes	17	14	31
Omentum	10	11	21
Pelvis	21	24	45
Peritoneum	18	12	30
Pleural effusion	4	8	12
Spleen	6	3	9
Time since last chemotherapy			
< 6 months	19	20	39
≥ 6 months	20	21	41
Histology			
Adenocarcinoma	1	0	1
Clear cell	1	0	1
Endometrioid	6	2	8
Serous	25	30	55
Other	6	9	15
Size of largest lesion			
≤ 50 mm	16	21	37
> 50 mm	23	20	43
Months from diagnosis			
Median	30	20	22
Range	8-151	4-57	4-151

Abbreviations: ECOG, Eastern Cooperative Oncology Group; OSI-211, liposomal lurtotecan.
*OSI-211 administered daily for 3 days.
†OSI-211 administered on days 1 and 8.

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of 1, and virtually all patients had disease measuring more than 20 mm.

Treatment Delivery

Patients in arm A received a median of five cycles of therapy (range, one to nine cycles), and patients in arm B received a median of three cycles (range, one to 14 cycles). In arm A, four of 37 patients receiving at least two cycles of treatment had their dose escalated compared with 18 of 36 patients in arm B. In terms of dose reductions, 15 patients were dose reduced in arm A, and nine were dose reduced in arm B.

Toxic Effects

All eligible patients were assessable for toxic effects (Table 3). The most common drug-related nonhematologic toxicities observed on treatment arm A (days 1, 2, and 3 schedule) were fatigue (79%), nausea (59%), alopecia (44%), vomiting (38%), anorexia (36%), stomatitis (31%), diarrhea (23%), and constipation (23%). The most common drug-related nonhematologic toxicities observed on treatment arm B (days 1 and 8 schedule) were nausea (71%), fatigue (68%), and vomiting (39%).

The frequency and severity of hematologic toxic effects were greater on arm A (Table 4). Of the 39 patients assessable for hematologic toxicity in arm A, 20 (51%) had grade 4 granulocytopenia during the course of therapy compared to only nine (22%) of 41 patients in arm B. This was accompanied by a greater frequency of febrile neutropenia; 10 patients (26%) in arm A had febrile neutropenia (one patient had a fatal episode of infection associated with neutropenia) compared with only one patient (2.4%) in arm B. Grade 3 or 4 thrombocytopenia was observed in 20 patients in arm A and 11 patients in arm B.

Three eligible arm A patients died while on study. The first patient who died developed bowel obstruction from disease progression and then neutropenic fever. She recovered from the latter but developed seizures related to cerebral metastases and died shortly afterwards. The second patient died as a result of cardiac failure during her second cycle of therapy. Autopsy revealed extensive coronary artery disease, and this event was deemed unlikely related to therapy. The third patient died on study as a result of peritonitis, which developed after paracentesis but quickly became serious because she was neutropenic after chemotherapy. The ineligible patient also died on study; she developed bowel obstruction from disease progression as well as treatment-related febrile neutropenia. Because of her progressive disease, she was not treated aggressively and died shortly thereafter.

Table 3. Nonhematologic Effects by Arm (related to drug)

	Treatment Arm A: Daily for 3 Days (n = 39)				Treatment Arm B: Days 1 and 8 (n = 41)			
	Any Grade		Grade 3 or 4		Any Grade		Grade 3 or 4	
Toxicity*	No.	%	No.	%	No.	%	No.	%
Fatigue	31	79	4	10	28	68	4	10
Anorexia	14	36	0	0	4	10	0	0
Nausea	23	59	2	5	29	70	3	7
Vomiting	15	38	2	5	16	39	2	5
Diarrhea	9	23	1	3	4	10	0	0
Constipation	9	23	0	0	4	10	1	2
Stomatitis	12	31	0	0	5	12	0	0
Alopecia	17	44	0	0	7	17	0	0
Febrile neutropenia	10	26	10	26	1	3	1	2

*Toxic effects reported as worst by patient.

Table 4. Hematologic Toxicity by Arm

	Treatment Arm A: Daily for 3 Days (n = 39)		Treatment Arm B: Days 1 and 8 (n = 41)	
Toxicity*	No.	%	No.	%
ANC				
Any	37	95	28	68
Grade 3	10	26	6	15
Grade 4	20	51	9	22
Platelets				
Any	35	90	22	54
Grade 3	18	46	10	24
Grade 4	2	5	1	2
HgB				
Any	39	100	40	98
Grade 3	5	13	4	10
Grade 4	3	8	2	5

Abbreviations: ANC, absolute neutrophil count; Hgb, hemoglobin.
*Toxic effects reported as worst by patient.

Tumor Response

Seven of the 80 eligible patients were not assessable for response assessment; in all cases, this was because disease was not reassessed after start of therapy for various reasons. Results of the response assessment, after independent radiologic review, are listed in Table 5. Of the 80 eligible patients, 24 had progressive disease, 41 had stable disease (median duration, 5.7 months), eight had responses to treatment confirmed by radiology review (one complete and seven partial responses), and seven were not assessable. One of the responding patients had a treatment-free interval of less than 6 months; the remainder had $\geq$ 6-month treatment-free intervals. Therefore, the overall response rate in the eligible patients was 10% (95% CI, 4.4% to 18.7%). There were six responses in arm A (response rate, 15.4% in eligible patients and 16.7% assessable patients) and two in arm B (response rate, 4.9% eligible in patients and 5.4% in assessable patients). Thus, in terms of the primary study end point, arm A was declared the winner, although it was clearly also more toxic.

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Table 5. Objective Tumor Response

Response	Treatment Arm A: Daily for 3 Days (n = 39)		Treatment Arm B: Days 1 and 8 (n = 41)	
	No. of Patients	Duration Range (months)	No. of Patients	Duration Range (months)
Complete response	1	13.5	0	—
Partial response	5	4.4-16.5	2	5.1-12.5
Stable disease	22	11.6-11.3	19	1.9-11.0
Progressive disease	8	—	16	—
Inassessable	3	—	4	—
Response rate, %	15.4		4.9	
95% CI	5.9-30.5		0.6-16.5	

Although the study was not powered to detect differences in progression-free survival, Figure 1 shows the time-to-progression curves by arm for randomly assigned patients. Results support the conclusion based on response rate that the daily for 3 days arm (arm A) was the winner.

Analysis of CA-125 response by the proposed Gynecologic Cancer Intergroup method was undertaken (Table 6), but only a handful of patients had the required double samples before starting OSI-211 that these criteria require for assessability. Therefore, a modified definition of the criteria was used in which only one sample $\geq 2 \times$ the upper limit of normal was required to consider a patient assessable for CA-125 response assessment. Using this definition, 55 patients were assessable (26 patients in arm A and 29 in arm B). In this subset, response rates were again higher on arm A (46%) than arm B (31%). Both rates were considerably higher than the objective response rate. This observation is interesting but of uncertain meaning.

Pharmacokinetic Results

Table 7 lists the pharmacokinetic results. As in the phase I experience with OSI-211, there was considerable interpatient variability in the plasma disposition of total lurtotecan. The AUC and C_{max} data derived after the first dose of each cycle were evaluated against the decrease in platelets and neutrophils at nadir using Spearman correlation analysis and the construction of scatter plots (data not shown). No relationship could be identified between AUC or C_{max} and granulocytopenia for either dose regimen. This was consistent with the phase I experience with this drug.[23]

DISCUSSION

The toxicities observed in this trial were similar to those seen with other nonliposomal topoisomerase I inhibitors, including previous studies with nonliposomal lurtotecan. Thus, the use of a liposomal formulation did not seem to have qualitatively changed the spectrum of toxicities.

This trial demonstrated that the response rate of OSI-211 in recurrent ovarian cancer was observed to be higher for the daily for 3 days schedule (six responses) than for the days 1 and 8 schedule (two responses), and thus, the 3-day schedule met the criteria to be considered the winner for purposes of further evaluation. The differences between the arms were not compared statistically. This result is similar to the result reported for topotecan,[10] where the repeated daily schedule (5 days) was found to be more active than the weekly 24-hour infusion.

In keeping with the tumor response outcomes, toxic effects, particularly myelosuppression, were more frequent and/or severe in arm A. This observation raises the question of whether the dose chosen for arm B was too low. The phase I data on which the recommended dose was based suggested that the dose-response relationship for myelotoxicity was quite steep; dose-limiting toxicity was observed at 2.8 and 3.2 mg/m^2/d, so it seems unlikely that a feasible increment in the starting dose used for arm B would

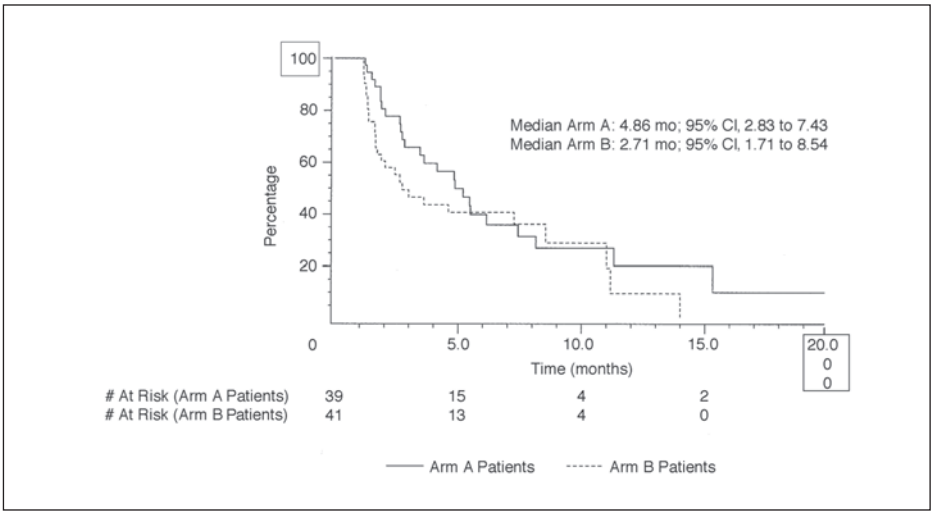

Fig 1. Progression-free survival for arm A (——) and arm B (- - - -). mo, months.

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Table 6. CA-125 Response by Treatment Arm

Treatment Arm	CA-125 Response: No — No. of Patients	No — %	Yes — No. of Patients	Yes — %	*P*
GCIG definition of CA-125 response, n = 22*					
Treatment arm A, n = 8	4	50	4	50	NS
Treatment arm B, n = 14	10	71	4	29	
Modified GCIG definition, n = 55†					
Treatment arm A, n = 26	14	54	12	46	NS
Treatment arm B, n = 29	20	69	9	31	

Abbreviations: GCIG, Gynecologic Cancer Intergroup; NS, not significant; UNL, upper normal limit.
*Proposed GCIG definition of CA-125 response to therapy of relapsed ovarian cancer at time protocol was written.[19] To be assessable for CA-125 response requires two pretreatment samples ≥ 2× UNL and at least two further samples after the start of treatment. A CA-125 response has occurred if, after two elevated levels before therapy, there is at least a 50% decrease that is confirmed by a fourth sample.
†Modified GCIG definition by investigators for purpose of this protocol. Patients with only one pretreatment CA-125 sample ≥ 2× UNL are included in analysis. All other criteria are the same as above.

be sufficient to increase the response rate to that seen in arm A. Furthermore, the protocol did incorporate a dose-escalation requirement in both arms. In fact, escalation to 2.8 mg/m^2/d in cycle 2 and beyond occurred in 50% of arm B patients who received at least two cycles of therapy. It is likely that further escalation would not have been possible when one also considers that the day 8 dose was to be withheld if the granulocyte count decreased below 1 × 10^9/L on that day. The problem of delivering sufficiently toxic doses is not uncommonly encountered in weekly regimens, in which not all drug is administered early in the cycle, and the occurrence of moderate toxicity precludes full delivery of drug on day 8. In summary, based on the toxicity information available, it is unlikely that substantially higher doses could be delivered with the days 1 and 8 schedule. Even if doses could have been consistently increased to a starting dose of 2.8 mg/m^2/d, it is improbable that this would have resulted in an increase in response rate sufficient (actual number of responses would have to increase from two, at present, to six or more) for that arm to become a winner in this trial design.

Table 7. Pharmacokinetic Results

Cycle 1, Dose 1 Data		AUC_{inf} (ng·hr/mL)		C_{max} (ng/mL)
Treatment arm A				
No. of patients	34		35	
Mean		4,818		893
SD		3,202		349
Median		4,526		986
Range		25-10,478		120-1,730
Treatment arm B				
No. of patients	31		32	
Mean		5,808		1,229
SD		4,047		466
Median		4,839		1,320
Range		495-13,206		373-2,105

Abbreviations: AUC_{inf}, area under the curve from time zero to infinity; C_{max}, maximal concentration; SD, standard deviation.

The other patient or disease factors that might influence response rate and thus lead to a difference in the outcome of the two arms, including time from last treatment, number of prior regimens, and histology, are relatively well balanced between the arms; in fact, patients were stratified by the first two factors. By chance, more patients in arm B than arm A had liver metastases at the time of study entry (15 *v* five patients, respectively), which could have had a negative impact on response outcomes. However, there were more patients with a performance status of 0 in arm B than arm A (12 *v* seven patients, respectively) and somewhat more patients in arm B than arm A with small tumor size (21 patients with tumors ≤ 5 cm *v* 16 patients with tumors ≤ 5 cm, respectively), which might have had the opposite impact.[4]

The original hypothesis behind developing the liposomal formulation of lurtotecan was that, with the resulting prolonged plasma exposure, one could avoid the need for repeated daily dosing and still retain meaningful efficacy. However, despite the prolonged exposure achieved clinically with OSI-211, this study does not show that it is possible to avoid the repeated daily dosing required for optimal activity of this topoisomerase 1 inhibitor; the weekly schedule was the loser in our study in terms of response rate. CA-125 response rates, time to progression, and overall survival data, although not powered to draw any comparative conclusions, are also consistent with this conclusion.

In conclusion, OSI-211 is a liposome-encapsulated topoisomerase I inhibitor with a substantially different pharmacokinetic exposure profile compared with the unencapsulated drug. OSI-211 has activity in advanced

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ovarian cancer comparable to that of other topoisomerase I inhibitors. The current study suggests that a repeat daily dose regimen will be necessary for optimal activity of this agent in ovarian cancer. Whether this agent has any advantage over topotecan is uncertain. A randomized trial to address this question has recently completed accrual.

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